Safety Data Sheet

Crown ethers

Division of Safety
National Institutes
of Health

WARNING!

COMPOUNDS IN THIS GROUP ARE TOXIC. THEY ARE ABSORBED THROUGH THE SKIN AND RESPIRATORY AND INTESTINAL TRACTS. THEY MAY CAUSE SEVERE IRRITATION OF TISSUES (SKIN, EYES, MUCOUS MEMBRANES, AND LUNGS). AVOID FORMATION AND BREATHING OF AEROSOLS OR VAPORS.

LABORATORY OPERATIONS SHOULD BE CONDUCTED IN A FUME HOOD, GLOVE BOX, OR VENTILATED CABINET.

AVOID SKIN CONTACT: IF EXPOSED, WASH WITH SOAP AND COLD WATER. AVOID WASHING WITH SOLVENTS. AVOID RUBBING OF SKIN OR INCREASING ITS TEMPERATURE.

FOR EYE EXPOSURE, IRRIGATE IMMEDIATELY WITH LARGE AMOUNTS OF WATER. FOR INGESTION, DRINK MILK OR WATER. REFER FOR GASTRIC LAVAGE. FOR INHALATION, REMOVE VICTIM PROMPTLY TO CLEAN AIR. ADMINISTER RESCUE BREATHING IF NECESSARY. REFER TO PHYSICIAN.

IN CASE OF LABORATORY SPILL, WEAR PROTECTIVE CLOTHING DURING CLEANUP. AVOID SKIN CONTACT OR BREATHING OF AEROSOLS OR VAPORS. USE WATER OR ORGANIC SOLVENTS TO DISSOLVE COMPOUND. USE ABSORBENT PAPER TO MOP UP SPILL. WASH DOWN AREA WITH SOAP AND WATER. DISPOSE OF WASTE SOLUTIONS AND MATERIALS APPROPRIATELY.

A. Background

Crown ethers are multidentate macrocyclic compounds, so called because of their appearance of space-filling models and their ability to "crown" cations. Their characteristic properties are their ability to solubilize inorganic compounds in organic solvents, and thus increase the range of their reactivities. The size of the cavity available in each crown ether varies and determines the type

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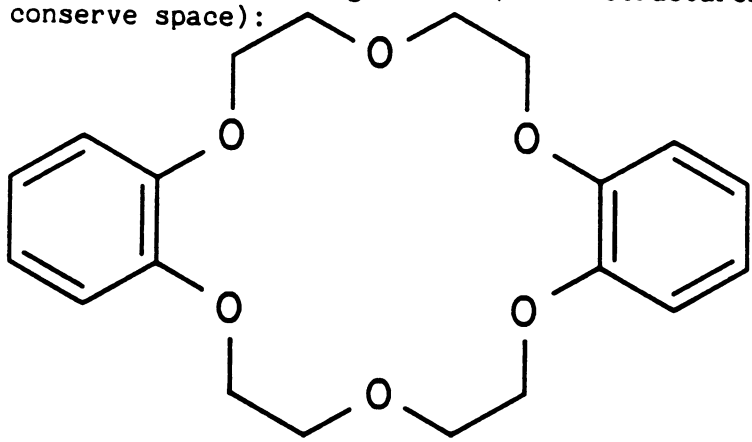
of cation which is bound most efficiently. Their primary uses are the solubilization of inorganic compounds just mentioned, separation of inorganic salts by use of the selectivity of various crown ethers, liquid-liquid extraction, liquid-membrane separation, ion-sensitive electrodes, and organic synthesis as phase transfer reagents.

This data sheet will deal mainly with simple crown ethers which are cyclic polyethers with the repeating unit $(-CH_2-CH_2-O-)n$ including however the dibenzo- and dicyclohexyl- crown ethers which were among the first synthesized (Pedersen, 1967) and which have found the widest application. Analogs in this series include "aza crowns" and "thia crowns" in which one (or more) oxygen atom is replaced by an NH or S group, respectively. Other members of this group include cryptands or cryptates (macrobi- or poly- cyclic compounds with crown-like bridges), lariat ethers (crowns with pendant donor groups), and crown esters.

Pertinent reviews include those of Christensen et al., 1974; Patai, 1980; Cawse et al., 1980; and Gokel and Korzeniowski, 1982.

Chemical and Physical Data

Nomenclature: The usual "shorthand" designation of crown ethers is m-crown-n where m = total number of atoms and n = number of hetero-atoms (usually oxygen) in the ring. Other substituents are named in the usual manner. The following structure will serve as a model for all crown ether designations (other structures will not be shown to conserve space):



dibenzo-18-crown-6

Individual data

12-crown-4 (Leong et al., 1974)

1. Chemical Abstract No: 294-93-9.

2. Synonyms: 1,4,7,10-tetraoxacyclododecane; EOCT; ethylene oxide cyclic tetramer.

3. Chemical formula and molecular weight: $C_8H_{16}O_4$; 176.24.

4. Boiling point: 238°C.

5. Volatility: vapor pressure = 0.03 mm Hg at room temperature.

6. Description: colorless liquid.

15-crown-5

1. Chemical Abstract No: 33100-27-5.

2. Synonym: 1,4,7,10,13-pentaoxacyclopentadecane.

3. Chemical formula and molecular weight: $C_{10}H_{20}O_5$; 220.30.

18-crown-6

1. Chemical Abstract No: 17455-13-9.

2. Synonym: 1,4,7,10,13,16-hexaoxacyclooctadecane.

3. Chemical formula and molecular weight: $C_{12}H_{24}O_6$; 264.36.

Dibenzo-18-crown-6

1. Chemical Abstract No: 14187-32-7

2. Synonym: dibenzo(b,k)(1,4,7,10,13,16)-hexaoxacyclooctadecin, 6,7,9,10,17,18,20,21-octahydro-.

3. Chemical formula and molecular weight: $C_{20}H_{24}O_6$; 360.

4. Melting point: 164°C, boiling point: 380-384°C at 679 mm Hg.

)icyclohexyl-18-crown-6

1. Chemical Abstract No: 16069-36-6.

2. Synonym: 2,3,11,12-dicyclohexyl-1,4,7,10,13,16-hexaoxacyclooctadecane.

3. Chemical formula and molecular weight: $C_{20}H_{36}O_6$; 372.

4. Melting point: 68.5-69.5°C for one isomer; the usual samples are mixtures of cis-trans isomers and have melting points between 36 and 56°C (Pedersen, 1967).

-crown-7

1. Chemical Abstract No: 33089-36-0.

2. Synonym: 1,4,7,10,13,16,19-heptaoxacycloheneicosane.

3. Chemical formula and molecular weight: $C_{14}H_{28}O_7$; 308.

24-crown-8

1. Chemical Abstract No: 33089-37-1.

2. Synonym: 1,4,7,10,13,16,19,22-octaoxacyclotetracosane.

3. Chemical formula and molecular weight: $C_{16}H_{32}O_8$; 352.

General data

1. Absorption spectroscopy: Ultraviolet, infrared, and NMR spectra of dibenzo- and dicyclohexyl-18-crown-6 have been published by Pedersen (1967), and chemical ionization mass spectra of a variety of others by van Gaever et al. (1978).

2. Solubility: There are practically no data. Pedersen (1967) states that dibenzo-18-crown-6 is slightly soluble in methanol (0.38 g/l at room temperature) and that "formic acid, chloroform, ethylene dichloride and pyridine are good solvents, ethers are poor, and alcohols and water very poor solvents" for this compound. However, ocular effects have been described which were produced by a 10% solution of dicyclohexyl-18-crown-6 in propylene glycol (Laidler and Stoddart, 1980). From a discussion of oral toxicity versus water solubility (without data for the latter) it may be inferred that water solubility increases with ring size in unsubstituted crown ethers (Hendrixson et al., 1978). 18-Crown-6 is said to be water-soluble (Noguchi et al, 1982).

3. Stability: Very few data, but it may be assumed that crown ethers are generally stable at ambient temperatures. 18-Crown-6, when heated to decomposition, emits acrid smoke and irritating fumes (Sax, 1984) and is rapidly (sometimes explosively) converted to p-dioxane at temperatures close to distillation temperatures (head temperature around 200°C) (Stott, 1976).

4. Chemical reactivity: The outstanding characteristic of crown ethers is their ability to incorporate inorganic cations in their cavity; the extent and specificity of this ability depends on the size of the cavity and of the cation. As an example, 15-crown-5 is highly specific for sodium, 18-crown-6 for potassium ion. An extensive table has been published by Liotta (1980). Amino acids (in the NH_3^+-form) are also complexed in a similar fashion by crown ethers (Noguchi et al., 1982).

5. Flash point: No data.

6. Autoignition temperature: No data.

7. Explosive limits in air: No data (but see B3, above).

Fire, Explosion and Reactivity Hazard Data

1. Fire fighting personnel should wear protective clothing and air-supplied respirators with full-face masks.

2. Crown ethers are probably incompatible with strongly oxidizing materials.

3. Hazardous decomposition products include dioxane which is irritating and toxic. Acrid smokes and irritating fumes are produced under conditions of fire.

4. Non-spark tools and equipment are not required.

Operational Procedures

It should be emphasized that this data sheet and the NIH Guidelines are intended as starting points for the implementation of good laboratory practices when using this compound. The practices and procedures described in the following sections pertain to the National Institutes of Health and may not be universally applicable to other institutions. Administrators and/or researchers at other institutions should modify the following items as needed to reflect their individual management system and current occupational and environmental regulations.

1. Chemical inactivation: No validated method reported.

2. Decontamination: Turn off equipment that could be affected by crown ethers or the materials used for cleanup. If there is any uncertainty regarding the procedures to be followed for decontamination, call the NIH Fire Department (dial 116) for assistance. Use absorbent paper to mop up spill. Wipe off surfaces with water or organic solvents, then wash with copious quantities of water. Glassware should be rinsed (in a hood) with organic solvents, followed by soap and water. Animal cages should be washed with water.

3. Disposal: No waste streams containing crown ethers shall be disposed of in sinks or general refuse. Surplus crown ethers or chemical waste streams contaminated with crown ethers shall be handled as hazardous chemical waste and disposed of in accordance with the NIH chemical waste disposal system. Nonchemical waste (e.g., animal carcasses and bedding) containing crown ethers shall be handled and packaged for incineration in accordance with the NIH medical-pathological waste disposal system. Potentially infectious waste (e.g., tissue cultures) containing crown ethers shall be disinfected by heat using a standard autoclave treatment and packaged for incineration, as above. Burnable waste (e.g., absorbent bench

top liners) minimally contaminated with crown ethers shall be handled as potentially infectious waste and packaged for incineration, as above. Absorbent materials (e.g., associated with spill cleanup) grossly contaminated shall be handled in accordance with the chemical waste disposal system. Radioactive waste containing crown ethers shall be handled in accordance with the NIH radioactive waste disposal system.

4. Storage: Store liquid and solid crown ethers and their solutions in tightly closed containers, preferably under refrigeration.

Monitoring and Measurement Procedures Including Direct Field Measurements and Sampling for Subsequent Laboratory Analysis

1. Sampling: No data.

2. Analysis. The only published procedure deals with thermometric titration of 18-crown-6 with barium perchlorate (useful range of crown ether = 1-100 mM in 2 ml), with examples of other crown ethers as well (Lamb et al., 1981). Crown ethers, particularly those containing chromogenic groups, have been used in the determination of inorganic cations (Nakamura et al., 1982; Yoshio and Noguchi, 1982) and it is possible that these procedures can be "turned around" for the analysis of crown ethers.

Biological Effects (Animal and Human)

1. Absorption: Crown ethers are absorbed by ingestion, inhalation and parenteral injection, and through the skin. Cyclohexyl-18-crown-6, on instillation in the eyes of rabbits, produces corneal injury and conjunctivitis but it is not known if it produces systemic effects by this route.

2. Distribution: No data.

3. Metabolism and excretion: No data.

4. Toxic effects: The acute oral LD50 in mice of 12-crown-4, 15-crown-5, and 18-crown-6 is 3-15, 1.02, and 0.71 g/kg, respectively (Hendrixson et al., 1978). It would appear from these few data that unsubstituted crown ethers are only moderately toxic, and that toxicity increases with ring size. The approximate oral lethal dose of dicyclohexyl-18-crown-6 in rats is 300 mg/kg, with death in 11 minutes. The dose-response curve for these compounds appears to be quite steep since 200 mg/kg of dicyclohexyl-18-crown-6 was not lethal in 10 days, and no cumulative toxicity was observed on administration of this compound at a level of 60 mg/kg/day to rats (Pedersen, 1967; reviewed by Laidler and Stoddart, 1980) or of 1/2 - 1/3 LD50 daily for 2 weeks of the three above-mentioned unsubstituted crown ethers to mice (Hendrixson et al., 1978). The per-cutaneous lethal dose of dicyclohexyl-18-crown-6 is 130 mg/kg

(Pedersen, 1967). The severity of symptoms (body tremors, respiratory impairment) decreases, and the length of time to onset of symptoms and to death increases, with increasing crown ether size among the three studied by Hendrixson et al. Sublethal doses of 18-crown-6 result in tremors, salivation, and hind leg paralysis in dogs (Takayama et al., 1977) and in rats and rabbits (Gad et al., 1978); these symptoms are reversible and disappear after discontinuance of dosage. A special study on the effects of inhalation of 0.5 or 1 ppm daily for 3 weeks of 12-crown-4 has shown marked testicular atrophy with degeneration of germinal epithelium which persisted for at least 4 months (Leong et al., 1974).

5. Carcinogenic effects: None reported.

6. Mutagenic and teratogenic effects: None reported.

Emergency Treatment

1. Skin and eye exposure: For skin exposure, remove contaminated clothing and wash skin with soap and water. Skin should not be rinsed with organic solvents. Since crown ethers are readily absorbed through the skin, avoid rubbing of skin or increasing its temperature. For eye exposure, irrigate immediately with copious quantities of running water for at least 15 minutes. Consider obtaining ophthalmological evaluation.

2. Ingestion: Drink plenty of water or milk. Refer for gastric lavage.

3. Inhalation: Remove victim promptly to clean air. Administer rescue breathing if necessary.

4. Refer to physician at once. Consider treatment for pulmonary irritation.

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